IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Art Unit | : | 1612 |
| Examiner | : | Barbara P. Badio |
| Applicant | : | Verlan H. VanRheenen |
| Appln. No. | : | 10/815,351 |
| Filing Date | : | April 1, 2004 |
| Confirmation No. | : | 8270 |
| For | : | CRYSTALLINE 19-NORSTEROIDS |

Dear Sir:

DECLARATION OF VERLAN H. VAN RHEENEN

I, Verlan H. Van Rheenen, hereby declare the following:

1. I am the inventor of the above-identified U.S. Patent Application No. 10/815,351, filed April 1, 2004, entitled "CRYSTALLINE 19-NORSTEROIDS."

2. I am currently the Vice President of Research and Development of Bridge Organics Company, the assignee of the above-identified U.S. Patent Application No. 10/815,351.

3. Bridge Organics Company is a research company engaged in the preparation of complex organic compounds and in the development of chemical processes for scale up. (Attached Exhibit A is a brochure describing Bridge Organics Co. and its services).

4. Prior to working for Bridge Organics Company, I was employed at Pharmacia & Upjohn, Kalamazoo, Michigan from 1966 to 1997. During my employment at Pharmacia & Upjohn, I was primarily engaged in research and development relating to steroid production, including synthesis and purification.

5. I earned by Doctor of Philosophy in organic chemistry from the University of Wisconsin, Madison, in 1966.

6. A copy of my circular vitae is attached hereto as Exhibit B.

7. I have read the Office Action dated August 3, 2007, in which all of the pending claims (1-4) of U.S. Application No. 10/815,351 were rejected under 35 U.S.C. §103(a) over Kim et al. (U.S. Patent Publication No. 2002/0025951 or WO 01/47945) in view of Berge et al. ("Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, January 1997, Vol. 66, No. 1).

8. I have read and understand the teachings of the applied Kim et al. and Berge et al. references.

9. The Office Action correctly states that the Kim et al. reference discloses the free base of the claimed hydrochloride and hydrobromide salts, and that the Berge et al. reference discloses that the characteristics of medicinal agents can be manipulated and optimized by converting a pharmaceutically active free base compound to a salt form.

10. It is my opinion that these disclosures would not have made the claimed compounds obvious to a person of ordinary skill in the art at the time the invention was made.

11. During my experiences as a scientist and researcher in the pharmaceutical arts, I have on occasion unsuccessfully attempted to convert a free base to a salt form. Based on these experiences, it is my opinion that it is not always obvious that any particular organic compound having pharmacological activity in its free base form can be converted into a salt form or into any particular salt form. Based on these experiences, I can further state that it is my opinion that the applied prior art references do not teach how to make the claimed salts, nor do they provide any expectation that the claimed salts can be made.

12. Based on my experience and education, it is my opinion that when a person of ordinary skill in the art desires to convert a base compound exhibiting a pharmaceutical activity into a salt form, the person of ordinary skill in the art will attempt to dissolve the free base in a solvent, add an acid compound, and employ some combination of cooling, stirring, seeding, or addition of an anti-solvent to induce precipitation of a salt. However, the outcome is not predictable, and success, if it is even possible, may depend on the solvent or solvents employed, the reagent selected to form the salt, the purity of staring material, and various other parameters, such as temperature and the degree of agitation.

13. I have unsuccessfully attempted to prepare the citrate, methane sulfonic acid, tartrate, and sulfate salts of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione. I am also personally aware of the numerous unsuccessful attempts of a former employee at Bridge Organics Company, Chiu Hong Lin, to make various other salts of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione. I have also had several unsuccessful attempts at preparing the claimed hydrochloride and hydrobromide salts.

14. My discovery of the claimed hydrochloride salt was not straight forward, and involved an unusual, and non-obvious combination of parameters. In particular, I discovered that when anhydrous hydrogen chloride in ether was added to the free base dissolved in ethyl acetate an oil deposit was formed. I further discovered that the oil deposit could be solubilized with acetone and re-formed as an oil by adding ether. I further discovered that the oil deposit could be redissolved in acetone, and that upon addition of ethyl acetate and ether, precipitation of

an amorphous solid occurred. Upon stirring at 40°C, the amorphous solid was slowly converted into a white, crystalline solid which was filtered and washed with ethyl acetate. Analysis showed that this crystalline solid was distinct from the starting free base material.

15. It is my opinion that the combination of steps, solvents, and parameters needed to made 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione hydrochloride is not obvious, and that the person of ordinary skill in the art would likely have become discouraged. In particular, it is my opinion that the person of ordinary skill in the art would have likely thought that the experiment was a failure upon formation of an oil deposit and would not have found it obvious to redissolve the oil deposit in acetone, add ethyl acetate, and add ether to cause precipitation of an amorphous material. Further, it is my opinion that the person of ordinary skill in the art would likely have regarded the precipitation of an amorphous material a failure and abandoned the experiment. Further, it is my opinion that the person of ordinary skill in the art would not have found it obvious to continue stirring the amorphous material in the combination of solvents at 40° to slowly convert the amorphous material to the claimed crystalline salt.

16. In the case of the hydrobromide salt, after various attempts resulted in the formation of an oil phase, crystals were finally obtained by dissolving the oil in acetone, adding ethyl acetate to the turbidity point, and then seeding with a trace of the previously isolated hydrochloride salt. This resulted in crystallization of the hydrobromide salt. Accordingly, I did not obtain the hydrobromide salt without first obtaining the hydrochloride salt by an unusual process that would not, in my opinion, have been obvious to a person of ordinary skill in the art.

17. From my experience, it is generally desirable to provide pharmaceutically active compounds in a crystalline form in order to facilitate economical purification, to establish quality criteria, and to achieve regulatory approval (i.e., FDA approval) of a commercially viable product.

18. In my experience, the ability to make a pharmaceutical product available to the benefit of the public often hinges on the discovery of a suitable crystalline salt form of the active ingredient. This, in my opinion, is the case with 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione which, in its free base form, is not crystalline. Clinical trials on human subjects strongly suggest that this compound is useful and highly beneficial when administered for the treatment of endometriosis, dysmenorrhea, endocrine hormone-dependent tumors, uterine fibroids, and endometrial proliferation.

19. However, it is my understanding that 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione cannot be exploited unless it can be made available in an economically purifiable form. Unless a pharmaceutical product can be made in an approved form at a reasonable price, it cannot be brought to market and it cannot be made available to the benefit of the public.

20. Hyun Kim et al. filed their first patent application disclosing 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione on May 1996. The antiprogestational activity of the compound and a method of making the compound were published in WO 97/41145 on November 6, 1997. Thus, those of ordinary skill in the art would have been aware of the compound and its purported utility in 1997.

21. It is also my opinion that those of ordinary skill in the art would have been aware of the desirability and need for providing 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione in a crystalline salt form. This is demonstrated by the Berge et al. reference, which describes advantages for providing a compound in a crystalline salt form.

22. It is also my opinion that a person of ordinary skill in the art would have understood that the discovery of a suitable crystalline salt form of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione would likely be critical in bringing a product to market that could benefit the public. In other words, it is my opinion that Kim et al. and those of ordinary skill in the art would have been aware of the urgent need to discover a suitable crystalline salt form of the compound, at least as early as about 1997.

23. It is my opinion that the very fact that the Kim et al. publication does not disclose a crystalline form of the compound suggests that Kim et al. were unable to discover a method of forming a crystalline form of the compound, since such crystalline form would have been advantageous for purification and testing purposes within the scope of their disclosure.

24. The recognized importance of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione is demonstrated by the subsequent efforts of Kim et al. to develop improved methods of making this specific compound, as indicated in WO 01/47945. This document is focused on achieving improved yield for the compound.

25. Since filing their first application in 1996, Kim et al. have filed five related applications in the United States alone. Despite a long recognized need for a suitable crystalline salt of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, none have been disclosed in the literature until Applicant's discovery of the hydrochloride and hydrobromide salts of this compound were disclosed on October 6, 2005 in U.S. Patent Application Publication No. 2005/0222109.

26. The Berge et al. reference only discloses the desirability of making crystalline salt forms of pharmaceutically active compounds, and does not enable those of ordinary skill in the art to make the salt forms. The Berge et al. reference merely discloses the 53 anions that had been employed in FDA approved commercially marketed salts as of January 1977. While the Berge et al. reference indicates that hydrochloride salts forms are the most utilized form, it does not disclose how to make the hydrochloride form of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione or any other active agent.

27. In my opinion, the person of ordinary skill in the art would not have known from the Kim et al. and Berge et al. references how to make the claimed hydrochloride or hydrobromide forms of the 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione compound disclosed by Kim et al.

28. It is my opinion that the approximately seven year period between the disclosure of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione by Kim et al. in 1997 and my discovery of the hydrochloride and hydrobromide forms of this compound in 2004 is evidence of a long-felt, but unfulfilled need for the claimed salts.

29. Further, it is my opinion that it can be reasonably inferred that Kim et al. and likely others, attempted, but failed to make the claimed crystalline salts or any other salt forms of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione. We (myself and others at Bridge Organics Co.) have also failed on many occasions over a period of years to successfully prepare a crystalline form of the free base.

30. The Berger et al. reference is concerned primarily with developing techniques for selecting the most appropriate salt form of a pharmacologically active compound when two or more forms of the compound of interest have already been discovered. It does not provide any teaching relevant to how such discovery of salt forms can be made.

31. Based on the teachings of Kim et al. in view of Berge et al., the person of ordinary skill in the art would not know whether 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione can be converted into a salt form, and if so which particular salt form(s), or how such salt form(s) might be made.

32. The combination of Kim et al. in view of Berge et al. establish an urgent need for a salt form of 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione, but do not provide any guidance toward how such salts may be prepared.

33. The combination of Kim et al. in view of Berge et al. establish the desirability of converting the 17α-acetoxy-21-methoxy-11β-(4-,N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione compound to a salt form. It is my opinion that the failure of Kim et al. to disclose a crystalline form of the compound is evidence that they were unable to make a crystalline form of the compound. These failures coupled with my own failures and that of my

colleague, Chiu Hong Lin, are evidence that the claimed salts would not have been obvious to a person of ordinary skill in the art.

The undersigned hereby declare that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

By: Verlan H. Van Rheenen
Verlan H. Van Rheenen

May 30, 2008
Dated

## KEY PERSONNEL BIOGRAPHIES

**Edward J. Hessler, Ph.D.**
*President*
Specialist in peptide, steroid and heterocyclic research.

**Harold A. Karnes, Ph.D.**
*Vice President, Sales*
Specialist in prostaglandins and heterocyclic research.

**Verlan Van Rheenan, Ph.D.**
*Vice President, R & D*
Specialist in steroid and prostaglandin research.

**Max E. Breuer, Ph.D.**
*Vice President, Engineering*
Specialist in separation processes and process development.

**David R. Buss, Ph.D.**
*Vice President, Finance*
Specialist in scaleup of complex reactions and fermentation isolations


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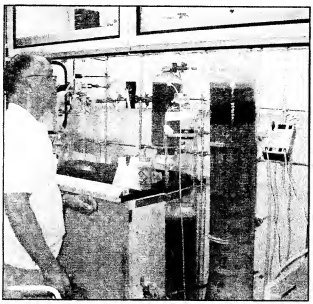
EXHIBIT A

# BRIDGE ORGANICS COMPANY

Bridge Organics is a research company engaged in preparation of complex organic compounds and in developing chemical processes for scaleup.

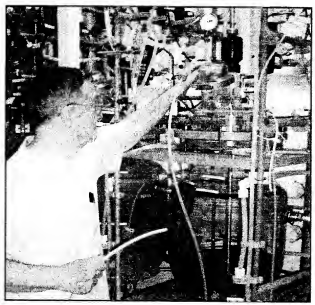


The company, which began operations in November 1997, was founded by retired scientists managers from Pharmacia & Upjohn. The founders had over 140 combined years of experience in chemical operations, first as scientists in process R&D and preparation laboratories, then as managers in chemical operations, including preparations, R&D, purchasing, chemical marketing, chemical production, and materials planning.

Bridge Organics is located in a 9,400 square foot R&D facility which is superbly suited for organic chemical and engineering research. Our equipment includes an HPLC, a 250 Mhz NMR spectrometer, a polarimeter, a GC, an ozone generator, and many low-temperature circulating coolers.

# PREPARATION SERVICES

The company's preparation service provides laboratory-scale chemicals of interest to pharmaceutical and biotechnology companies. We can provide batches up to 10 kg or more, with typical purities of 98%. These products, made through complex multi-step laboratory processes, include metabolites, analytical impurities, research materials, stable isotope-labeled chemicals, and chemical library replacements or additions. We have 2 x 50 Liter workcenters, and 1 x 25 Liter workcenter.



Normally, a customer provides an approximate procedure for the reaction sequence, with or without a secrecy agreement (as preferred by the customer).

# PROCESS R&D SERVICES

Our scientist are specialists in the design, development and engineering of chemical processes for scaleup purposes. We offer this service to those companies who would like to develop a new process or would like to improve their particular process for manufacturing a chemical (primarily to increase capacity or reduce costs), but who do not have R&D personnel available for such a task. For R&D services, a customer typically provides available process information through a secrecy agreement.

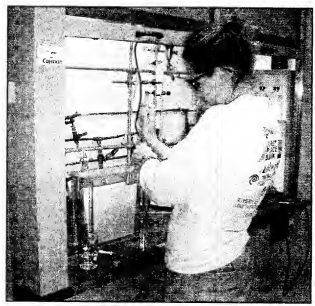



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EXHIBIT B


## *VERLAN VAN RHEENEN, PH.D.*

2117 SHEFFIELD

KALAMAZOO, MI 49001

269-226-9660


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**BRIDGE ORGANICS CO.**

Vice President of Research and Development 1998-current

Experience in many areas of organic synthesis.

**UPJOHN CAREER SUMMARY**

Extensive experience in primary (API) manufacturing: first as a scientist, designing and developing novel practical processes for Production at Pharmacia & Upjohn, and more recentlyn R&D management, concentrating on resource allocation, project management, regulatory compliance, and validation.

**Experience and Accomplishments**

Pharmacia & Upjohn, Kalamazoo, Michigan 1966-1997

*Director, Chemical Process R&D (1984-1997)*

- Directed a group of 70-75(~24 Ph.D. scientist-led groups) responsible for design, development, engineering and piloting chemical processes, and installation and maintenance of these processes in a Production Plant.
- Introduced new manufacturing process for many steroid products, both old and new, that transformed P&U steroid technology to one based on sitosterol as raw material.
- Designed and introduced the first manufacturing process for a cephalosporin at Upjohn.
- Actively involved in the design and the construction of a state-of-the-art building for CPR&D. This $20MM project was concluded under budget.
- Devised a Validation Plan for completing Process Qualification (PQ) for over 100 API's being manufactured at P&U.
- Set up an R&D-based Validation Team who devised the work processes and documentation required to satisfy the regulation for PQ and then did the document

preparation and coordination of the Validation Exercise to accomplish the Validation Plan.

- Set up a Process Safety Management system and team to provide the documentation (Process Safety Information Report) to satisfy the OSHA directive and assist in HAZOP analysis for Operational Qualification (OQ).
- Set up a team-based Project Management system for coordination of the many regulatory and logistical issues surrounding a successful API development and manufacturing startup, promoting interaction with other Project Management areas and clear delineation of the responsibilities with line management.
- Introduced Customer Service as a potent marketing tool for the Pharmaceutical Chemical Business

*Director, chemical preparations (1992-1993)*

Responsible for a group of 34 (~20 scientists) and the Pilot Plant who supplied all APIs needed for preclinical and clinical testing of human and animal hearth products.

***Distinguished Scientist V (1977-1984)***

- Appointed to the first group of scientists to attain this rank. Remained on the Scientist V committee by appointment throughout my managerial career.
- Developed numerous processes to transform P&U's steroid processing to the sitosterol raw material base.
- Served twice as Interim Associate Director-Chemical Process R&D (1974-1975 and 1983-1984), taking responsibility for a Chemical Section (7-8 Ph.D.-led groups) concurrently with maintaining my chemical laboratory.

***Scientist I through Scientist IV (1966-1977)***

- Developed novel and economically superior chemical processes for existing products including medroxy progesterone-Provera ®, methyl prodnisolone-Medrol ®, progesterone, prednisolone-Deltasone ®.
- Developed processes for new proprietary products including prostaglandin total synthesis for PGF2a (Prostin F2a®) , PGE2 (Prostin E2® , Dinoprostone®), PGE1 (Prostin VR®, Caverject®), 15a-methyl PGF2a (Methaprost®), and Ibuprofen (Motrin ®).
- Continued involvement through engineering, piloting, plant introduction, and maintenance and improvement of the plant process for the life of the product. See the Publication section for a scientific account of these projects.

## Publications


Verlan H. Van Rheenen, "Approaches to a Synthesis of Miroestrol," Ph.D. Thesis, University of Wisconsin , 1966.

Hans Muxfeldt, Manfred Weigele, and Verlan Van Rheenen, "Magnesium Methoxide Cyclization of Biacetyl Derivatives," *J. Org. Chem.* **30** , 3573 (1965).

Verlan Van Rheenen, "Copper Catalyzed Oxygenation of Branched Aldehydes--An Efficient Ketone Synthesis," *Tetrahedron Letters* , 985 (1969).

V. Van Rheenen, "Copper-catalyzed Oxygenation of Enamines, " *Chem. Comm.,* 314 (1969).

Robert C. Kelly, Verlan Van Rheenen, I. Schletter, M.D. Pillai, "Prostaglandin Synthesis. I. An Improved Synthesis Through Bicyclo[3.1.0]hexane Intermediates," *J. Amer. Chem. Soc.,* **95**, 2746 (1973).

R. Kelly and V. Van Rheenen, "Prostaglandin Synthesis. II. A Novel Resolution of Aldehyde and Ketone Intermediates," *Tetrahedron Lett.,* 1709 (1973).

R. Kelly and V. Van Rheenen, "Prostaglandin Synthesis III. An Improved Opening Of Bicyclo[3.1.0]hexane Intermediates." *Tetrahedron Lett., 1067 (1976).*

V. Van Rheenen, R.C. Kelly and D.Y. Cha, "An Improved Catalytic OsO4 Oxidation of Olefins to cis-1,2-Glycols Using Tertiary Amine Oxides as the Oxidant," *Tetrahedron Lett.* 1973 (1976).

V. Van Rheenen, D.Y. Cha, and W.M. Hartley, "Catalytic Osmium Tetroxide Oxidation of Olefins: Preparation of cis-1,2-cyclohaxanediol," *Organic Synthesis,* **58,** 43 (1978).

Verlan Van Rheenen, K. Paul Shephard, "New Synthesis of Cortico Steroids from 17-Keto Steroids: Application and Stereochemical Study of the Unsaturated Sulfoxide-Sulfenate Rearrangement" *J. Org. Chem.,* **44,** 1582 (1979).

# US Patents

Joel E. Huber, Verlan H. Van Rheenen, "16α-Methylation of Corticoids" *USP 4990612* (1991)

Joel E. Huber, Verlan H. Van Rheenen, "16α-Methylation Process--Copper Catalysis, Silation" *USP 4929395* (1990).

Joel E Huber, Verlan H. Van Rheenen, "16 α- Methyl-17α- 20-Epoxysteroid and Process" *USP 4891426* (1990).

Verlan H. Van Rheenen, "11β,17α-Dihydroxy-17β-Cyano Androstanes" *USP 4831113* (1989).

Verlan H. Van Rheenen, "Steroids Having an Enamide, or Cyano and Their Use" *CA 105:60816 (US-576590).*

Joel E. Huber ,Verlan H. Van Rheenen, "16α-Methylated-Δ17(20)-Corticoids as Intermediates" *USP 4704455 (1987)*

Verlan H. Van Rheenen "Ethynylation Of 16-Methylene-17-Keto Steroids" *USP 4614621* (1986).

Verlan H. Van Rheenen, "Cyanohydrin Process--Intermediates for Corticoids" *USP 4585590* (1986).

Verlan H. Van Rheenen, " 16-Methylene-17α-Hydroxy-Progesterones" *USP 4567001* (1986).

Verlan H. Van Rheenen, "Cyanohydrin Process" *USP 4548748* (1985).

Verlan H. Van Rheenen, Dae Y Cha, "Process to Prepare Stabilized Monolithiun Acetylide" *USP 4526720 (1985)/*

Verlan H. Van Rheenen "Spironolactone Process" *USP 4501695* (1985).

Verlan H. Van Rheenen, "Cyanohydrin Process Intermediates" *USP 4500461* (1985).

Verlan H. Van Rheenen, Joseph M. Timko, "16β-Methyl Steroid Process" *USP 4451404* (1984).

Verlan H. Van Rheenen , "Isomerization--Acylation Process" *USP 4443377* (1984).

Verlan H. Van Rheenen, "Process for Preparing 16-Methylene Steroids", *USP 441682 (1983).*

Edward J Hessler, Verlan H. Van Rheenen, "Synthesis of 16-Unsaturated Pregnanes from 17-Keto Steroids", *USP 4216159,* (1980).

Verlan H. Van Rheenen, "Preparing 2-Arylalkanoic Acid Derivatives" *USP 4189596* (1980).

James B. Heather, Verlan H. Van Rheenen, "Phosphate-Catalyzed Acylation of Steroidal Tertiary Alcohols" *USP 4154748* (1979).

Verlan H. Van Rheenen, "Process for Preparing a 2(R) or 2(S) Tricyclic Lactone Glycol--Prostaglandins" *USP 4061657* (1977).

Keneth Paul Shephard, Verlan H. Van Rheenen, "Process for the Preparation of 17α-Hydroxy Progesterones and Corticoids from Androstenes" *USP 4041055* (1977).

Verlan H. Van Rheenen "Lactone Intermediates for Prostaglandins" *USP 3965118* (1976).

Verlan H. Van Rheenen "Tricyclic Lactone Glycol Sulfonates--Prostaglandins" *USP 3953473* (1976).

Verlan H. Van Rheenen "Bicyclic Lactones--Prostaglandins" *USP 3880887* (1975).

V. Van Rheenen, "Process for Preparing Lactone Intermediates" *USP 3823138* (1974).

Verlan H. Van Rheenen, "Conversion of 3-Enol Ethers of 3-Keto Steroids to the Corresponding 3-Keto-Δ4, 6β-(N,N-disubstituted)-Amino Methyl Compounds" *USP 3702848* (1972).

John M. Beaton, Jekishan R. Parikh, Verlan H. Van Rheenen, "Process for the Selective Reduction of 6-Methylene-3-Keto-Δ4-Steroids" *USP 3679715* (1972).

Verlan H. Van Rheenen, "Novel Chemical Process --Copper Catalyzed Oxygenation of Enamines" *USP 3661942* (1972).

Verlan H. Van Rheenen, "Process for the Conversion of 3-Enol Ether Steroids to the Corresponding 3-Keto-Δ4-6-Methylene Compounds" *USP 3642840* (1972).

Verlan H. Van Rheenen, "Steroidal 3-Keto-Δ1,4- Enamines" *USP 3629298* (1971).

Verlan H. Van Rheenen, "Process for the Preparation of Enol Ethers of 6-(N,N-Dimethyl Amino)-Methyl Steroids", *USP 3580935* (1971).

Verlan H. Van Rheenen, "Oxidation of Aldehydes to Ketones Employing Copper ions as Catalysts" *USP 3496197 (1970).*

## Education

Ph.D., Organic Chemistry , University of Wisconsin, Madison, 1966.
B.A., Chemistry, Central College, Pella, Iowa, 1961.